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Famotidine polymorphic transformation in the grinding process significantly depends on environmental humidity or water content

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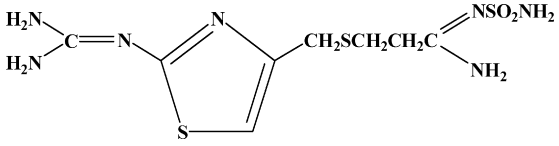
Abstract

The effect of environmental humidity and additional water added on the polymorphic change of famotidine in the process of grinding was investigated. The famotidine form B powder with or without additional amount of water added was respectively ground for 30 min in an oscillatory ball mill under 25 ± 2 °C and three relative humidities (RH) (50 ± 5%, 75 ± 5% or 95 ± 5% RH). Each ground sample was periodically isolated for analytical determinations by using differential scanning calorimetry (DSC), thermogravimetric (TG) analysis and Fourier transform infrared (FT-IR) microspectroscopy. The results indicate that the higher environmental humidity might induce and promote the polymorphic transformation of famotidine from form B to form A in the process of grinding. Moreover, the more the amount of water externally added the easier the polymorphic transformation of famotidine from form B to form A obtained. In addition, the more grinding time spent the more formation of form A obtained. This study disavowed the results of other studies in which no polymorphic change of famotidine even by grinding. The apparent evidence shows that the solid-state polymorphic transformation of famotidine from form B to form A in the grinding process significantly depended on the relative humidity of atmosphere and the additional amount of water added.

Keywords: Famotidine; Grinding; Polymorphic transformation; Humidity; Water content; FT-IR; DSC/TG

1. Introduction

Famotidine with a trade name of Pepcid® is a famous third generation of an H_2-receptor blocker for the treatment of gastrointestinal ulcers. There are two polymorphs for famotidine, forms A and B, with monotropic behavior (Hegedus et al., 1989; Echizen and Ishizaki, 1991; Hassan et al., 1997); polymorphic A is the thermodynamically more stable form but polymorphic B is the kinetically favored form with more pharmacological activity than form A. The active pharmaceutical ingredient (API) of famotidine commercialized in the market is form B, which has been concerned by FDA due to their physical properties, solubility, bioavailability or bioequivalence of different polymorphic forms (Yu et al., 2003; Snider et al., 2004). A patent infringement suit of famotidine polymorph had been made a sound legal argument (Takenaka, 2002; Kovac, 2001; Trask, 2007), suggesting the importance of solid-state polymorphism of famotidine in the pharmaceutical industry.



The grinding process is well known to be one of the possible manufacturing procedures in the pharmaceutical industry (Morris et al., 2001; Zhang et al., 2004). The energetic input of solid-state grinding has been reported not only to alter the particle size, surface area and/or crystallinity of the drug but also to induce a variety of solid-state polymorphic conversion of drug, resulting in the modification of physical and chemical properties of drugs to finally influence the bioavailability of a drug through the rate of dissolution (Yu et al., 2004; Singhal and Curatolo, 2004; Datta and Grant, 2004; Chawla and Bansal, 2004).

Although the grinding process may easily cause the transition of a metastable drug into the stable phase (Vippagunta et al., 2001; Brittain, 2002; Chawla and Bansal, 2004), the effect of grinding process on the polymorphic transformation

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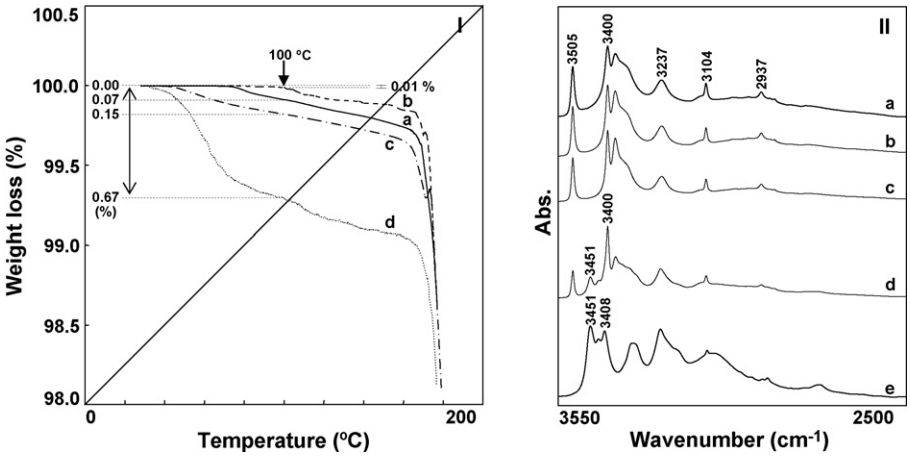

Fig. 1. TG curves (I) and FT-IR spectra (II) of the 30 min-ground famotidine under three different environmental RH conditions. Key: Intact famotidine without grinding: (a) form B; (e) form A. 30 min-ground famotidine form B under three different environmental RH conditions: (b), 50 ± 5% RH; (c) 75 ± 5% RH; (d) 95 ± 5% RH.

of famotidine was scarcely studied. Until now, several studies had indicated that no polymorphic change was observed even by grinding process. Only the reduction of melting point of form B due to a change in particle size was found via grinding (Hassan et al., 1997; Roux et al., 2002; Német et al., 2005). The grinding-induced polymorphic transformation of famotidine from form B to form A had been successfully examined in our previous studies (Lin et al., 2006; Cheng et al., 2007), but this polymorphic change of famotidine did not always occur via grinding. Based on the above uncertain results, the reason of poor reproducibly polymorphic transformation of famotidine in the process of grinding is worthy of further investigation.

Detailed retrospect on the research condition of our successful study, from the record we found that during the experimental date the climate was always wet. It is doubtful whether the humidity or water content absorbed may relate to the possibility of the polymorphic change of famotidine in the process of grinding. In this study, the effect of environmental humidity and additional water added on the polymorphic change of famotidine in the process of grinding was investigated. We report herein the environmental humidity and water content in famotidine played an important role to promote the ability of grinding-induced polymorphic transformation of famotidine polymorph.

2. Experimental

2.1. Materials

A pharmaceutical grade of famotidine form B was used. The organic solvents used were of analytical reagent grade without further purification. Polymorphic forms A and B of famotidine were prepared by recrystallization from acetonitrile and methanol, respectively (Hegedus et al., 1989; Echizen and Ishizaki, 1991; Hassan et al., 1997; Lin et al., 2006, 2007).

2.2. Preparation of different ground samples

2.2.1. Effect of environmental humidity

The raw material of famotidine form B powder (water content: 0.07%, w/w) was respectively ground for 30 min in an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany) at an oscillation frequency of 20 Hz. Each 0.2 g form B powder was placed in a 10 ml volume agate milling jar containing two 10 mm diameter agate balls. The grinding process was operated in the experimental room by controlling it at 25 ± 2 °C and three relative humidities (RH) (50 ± 5%, 75 ± 5% or 95 ± 5% RH).

2.2.2. Effect of additional amount of water added

The form B powder after adding a certain amount of water (weight ratio of water:famotidine: 0.1:1, ∼0.2:1, w/w) was also ground in an oscillatory ball mill for 30 min under 25 ± 2 °C/75 ± 5% RH condition. In addition, the powder sample with weight ratio of water to form B (0.15:1, w/w) was ground for different grinding times. At predetermined intervals, each ground sample was periodically isolated for further analytical determination.

2.3. Analytical identification

All the ground samples were immediately determined by Fourier transform infrared (FT-IR) microspectroscopy (Micro-FT-IR 200, Jasco Co., Tokyo, Japan) with one KBr method by transmission technique (Lin et al., 2002; Lin and Chien, 2003; Wang et al., 2007), differential scanning calorimetry (DSC) and thermogravimetric (TG) analysis at a heating rate of 3 °C/min with an open pan system (TA Instruments Inc., New Castle, DE, USA) in a stream of N_2 gas from 30 to 200 °C. Polymorphic forms A and B of famotidine were also confirmed by the above analytical instruments. All the TG analyses were performed in triplicate to provide mean values.

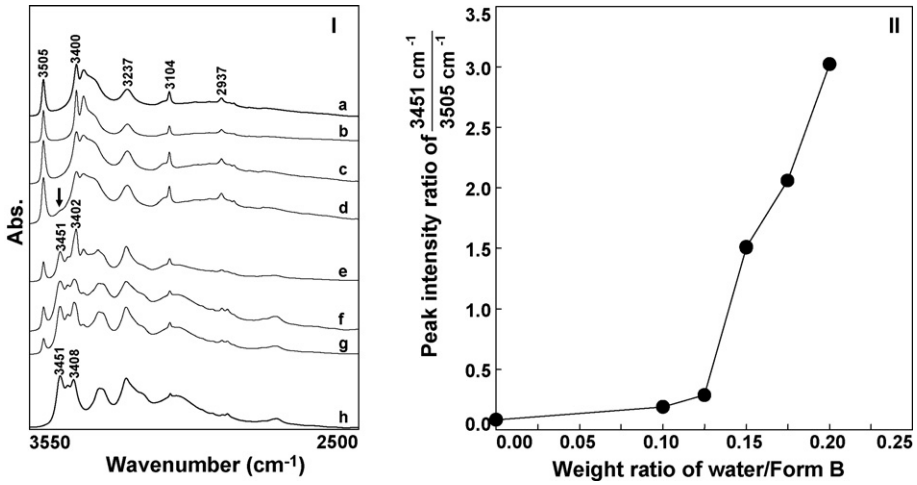

Fig. 2. The effect of amount of water added on the FT-IR spectral change (I) and the peak intensity ratio of 3451/3505 cm^{-1} (II) of famotidine after 30 min grinding. Key: Intact famotidine without grinding: (a) form B; (h) form A. 30 min-ground famotidine form B with different weight ratios (w/w) of water to famotidine form B: (b) 0:1; (c) 0.1:1; (d) 0.125:1; (e) 0.15:1; (f) 0.175:1; (g) 0.2:1.

3. Results and discussion

3.1. Effect of environmental humidity on the polymorphic transformation of famotidine

Fig. 1 shows the TG curves and FT-IR spectra of the 30 min-ground famotidine samples under three different environmental RH conditions. The raw material of form B without grinding had 0.07% (w/w) of water content. It is apparent that the water content of the 30 min-ground form B sample under the $75 \pm 5\%$ RH or $95 \pm 5\%$ RH condition was, respectively, increased from 0.07 to 0.15% (w/w) or to 0.67% (w/w), respectively, but it was decreased from 0.07 to 0.01% (w/w) under $50 \pm 5\%$ RH condition. The increase of water content for the ground form B sample might be due to the water vapor adsorption from atmosphere during the grinding process (Otsuka and Matsuda, 1993; Ohta et al., 2000; Wongmekiat et al., 2003). When form B was ground for 30 min under $50 \pm 5\%$ RH condition, on the other hand, the water content contained in the ground form B sample was reduced from 0.07 to 0.01% (w/w), due to the dehydration of water in the dry grinding condition.

In our previous study (Lin et al., 2006, 2007), two peaks at 3505 and 3400 cm^{-1} assigned to the asymmetric and symmetric stretching NH_2 groups were observed in the FT-IR spectrum of form B (Fig. 1-a), but two peaks at 3451 and 3408 cm^{-1} were corresponded to the form A (Fig. 1-e). Because there was no other interference for both peaks at 3451 and 3505 cm^{-1} in the range of 3550–3300 cm^{-1}, thus both peaks might be acted as a fingerprint-marker to differentiate the polymorphs A and B of famotidine. Here, the FT-IR spectrum of the 30 min-ground form B sample under the $50 \pm 5\%$ RH or $75 \pm 5\%$ RH condition was the same as that of the FT-IR spectrum of form B without grinding. However, a peak at 3451 cm^{-1} was found in the FT-IR spectrum of the 30 min-ground form B sample under $95 \pm 5\%$ RH. The appearance of 3451 cm^{-1} might be due to the polymorphic transformation from form B to form A. The results of TG curve and FT-IR spectra strongly support that the higher environmental humidity might induce and promote the polymorphic transformation of famotidine from form B to form A during the process of grinding.

3.2. Additional amounts of water added affecting the polymorphic transformation of famotidine

In order to test and verify whether water content in the sample might availably induce the polymorphic transformation of famotidine, the additional water was added to the form B powder and ground for 30 min. The effect of amount of water added on the

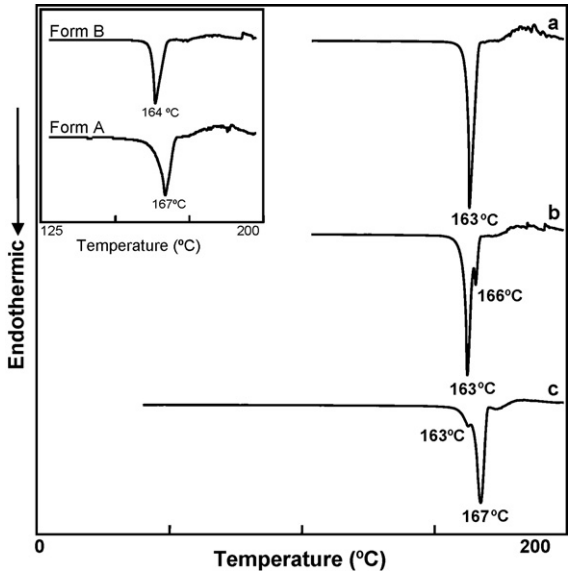

Fig. 3. DSC thermograms of intact famotidine forms A and B, as well as the different famotidine ground samples (a–c). Key: 30 min-ground famotidine form B with different weight ratios (w/w) of water to famotidine form B: (a) 0:1; (b) 0.1:1; (c) 0.2:1.

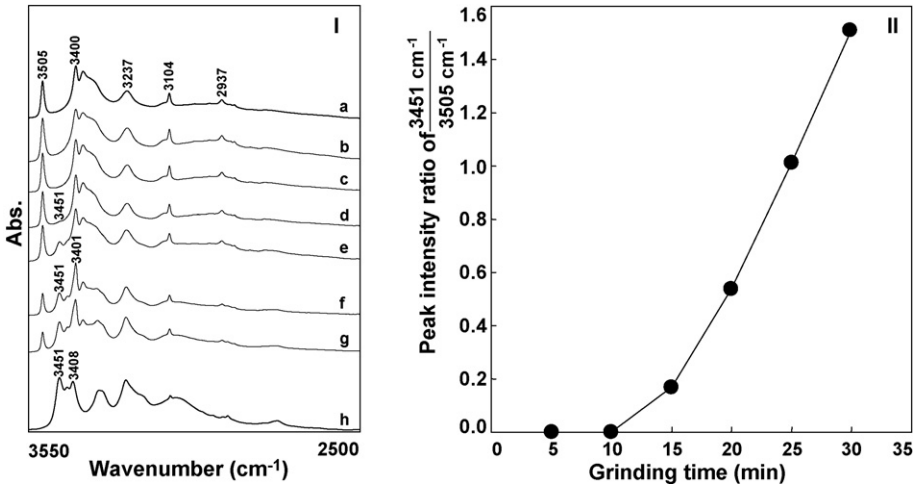

Fig. 4. The grinding time affecting the FT-IR spectral change (I) and the peak intensity ratio of 3451 cm^{-1}/3505 cm^{-1} (II) of different famotidine ground samples. Key: Intact famotidine without grinding: (a) form B; (h) form A. Grinding time for samples with the same weight ratios (0.15:1, w/w) of water to famotidine form B: (b) 5 min; (c) 10 min; (d) 15 min; (e) 20 min; (f) 25 min; (g) 30 min.

FT-IR spectral change and the peak intensity ratio of 3451 cm^{-1} (form A)/3505 cm^{-1} (form B) of 30 min-ground form B sample is shown in Fig. 2. It clearly indicates that the FT-IR peak at 3451 cm^{-1} assigned to form A appeared from the 0.125:1 (w/w) of weight ratio of water to form B. From this weight ratio, the peak intensity at 3505 cm^{-1} was decreased whereas the peak intensity at 3451 cm^{-1} was increased. The peak intensity ratio of 3451/3505 cm^{-1} of the ground form B sample was markedly increased with the increase of weight ratio of water to form B, suggesting that the 0.125:1 (w/w) weight ratio of water to form B was a critical point. Beyond this weight ratio, the formation of famotidine form A transformed from form B was significantly pronounced.

Fig. 3 shows the DSC thermograms of famotidine forms A and B, as well as the different 30 min-ground form B samples. There was an endothermic peak at 167 °C for famotidine form A and at 164 °C for famotidine form B by using DSC determination with 3 °C/min. When form B without adding water was ground alone for 30 min, an endothermic peak at 163 °C was still observed, indicating no any polymorphic transformation induced by grinding under 25 ± 2 °C/75 ± 5% RH condition. Once the water was additionally added to form B (water:form B = 0.1:1, w/w) and then ground for 30 min, a domain endothermic peak at 163 °C for form B and a small peak at 166 °C for form A were respectively found in its DSC thermogram. However, the IR spectrum of form A was not detected in Fig. 2c. The marked difference may be due to the effect of temperature during the DSC measurement on the crystal nucleus of form A being existed in the process of grinding, in which did not detect in the IR spectrum. This speculation may consist with the fact that form A is thermodynamically more stable (Hegedus et al., 1989; Echizen and Ishizaki, 1991; Hassan et al., 1997). By further addition of water to form B (water:form B = 0.2:1, w/w), a small endothermic shoulder at 163 °C and a sharp peak at 167 °C were observed. The former shoulder might be due to the form B and the latter sharp peak was attributed to the form A. Here, both peaks for famotidine forms A and B simultaneously appeared in DSC thermogram were the first report. This suggests again that the amount of water added might significantly cause the polymorphic transformation of famotidine from form B to form A.

3.3. *Effect of grinding time on the polymorphic transformation of famotidine*

The grinding time affecting the FT-IR spectral change and the peak intensity ratio of 3451/3505 cm^{-1} of different famotidine ground samples is shown in Fig. 4. The sample with a constant weight ratio (0.15:1, w/w) of water to form B was used and ground for different grinding times. With the increase of grinding time, the peak intensity at 3505 cm^{-1} for form B was slowly reduced but the peak intensity at 3451 cm^{-1} for form A was gradually increased. The peak intensity ratio of 3451/3505 cm^{-1} for the ground form B sample was markedly increased after grinding for 10 min, suggesting that the grinding time might play an important role to induce the formation of famotidine form A. The more grinding time spent the more formation of form A obtained.

This paper first reports the water contained in famotidine form B powder provides an important role to promote the grinding-induced polymorphic transformation of famotidine polymorph. The mechanism for water-promoted polymorphic transformation of famotidine from B in the grinding process may be proposed as follows: the increase of specific surface area and/or more amorphization of famotidine produced by 30 min-grinding process might easily cause the water vapor adsorption or moisture uptake from atmosphere (Otsuka and Matsuda, 1993; Ohta et al., 2000; Wongmekiat et al., 2003). Moreover, during the process of grinding either water vapor adsorption or additional water added seemed to directly reduce the glass transition temperature and/or indirectly decrease the onset of nucleation of the ground famotidine, resulting in the promotion of polymorphic transformation of famotidine from form B to form A via recrystallization (Ford and Timmins, 1989; Chieng et al., 2006).

4. Conclusion

From this study, the environmental humidity of operation condition and the residual water content in famotidine should be well controlled to prevent the polymorphic transformation of famotidine polymorph in the grinding process of pharmaceutical manufacturing.

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